

10/536356

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
17 June 2004 (17.06.2004)

PCT

(10) International Publication Number
WO 2004/050698 A3

- (51) International Patent Classification⁷: **C07K 14/47**, A61K 49/14, 47/48, A61P 35/00
- (21) International Application Number: PCT/EP2003/013413
- (22) International Filing Date: 28 November 2003 (28.11.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 02026700.1 29 November 2002 (29.11.2002) EP
- (71) Applicant (*for all designated States except US*):
**DEUTSCHES KREBSFORSCHUNGSZENTRUM
STIFTUNG DES ÖFFENTLICHEN RECHTS**
[DE/DE]; Im Neuenheimer Feld 280, 69120 Heidelberg (DE).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **HECKL, Stefan**
[DE/DE]; Steubenstrasse 28, 69120 Heidelberg (DE).
BRAUN, Klaus [DE/DE]; Bruchhausen 20, 69207
Sandhausen (DE). **PIPKORN, Rüdiger** [DE/DE];
Adolf-Rauch-Strasse 3, 69124 Heidelberg (DE).
WALDECK, Waldemar [DE/DE]; Tilsiter Strasse
49, 69514 Laudenbach (DE).
- (54) Title: **PEPTIDE CONJUGATE USEFUL FOR CELL NUCLEUS MOLECULAR IMAGING AND TUMOR THERAPY**
- (57) Abstract: Described is a conjugate comprising (a) an amphiphilic transport peptide of human origin as a transmembrane module (TPU), (b) a nuclear localization sequence (NLS) and (c) a signalling and/or drug carrying module (SM), preferably comprising Gd, Ga, Fe, Mn, I and/or F as (diagnostic) image creating compound. Said conjugate is useful for diagnostic purposes, e.g., for cell tracking by MRI, as a contrast agent (e.g., replacing a "biopsy clip") for MRI, or for determining the activity of DNA repair enzymes by MRI. Said conjugate is also useful for therapy, e.g., for chemotherapy or intranuclear Gadolinium Neutron Capture Therapy (GNCT). The transmembrane module (TPU) is selected among peptides of human origin, whose amino acid sequences are similar to the sequence of the antennapedia fragment RQIKIWFQNRRMKWKK. In a specific embodiment, TPU is derived from the human homeobox protein HOX-B1. The nuclear localization sequence (NLS) is derived from the simian virus 40-T antigen or from a transcription factor.
- (74) Agent: **SCHÜSSLER, Andrea**; Huber & Schüssler, Truderinger Str. 246, 81825 München (DE).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*
- (88) Date of publication of the international search report: 20 January 2005
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 2004/050698 A3

INTERNATIONAL SEARCH REPORT

International Application No.

EP 03/13413

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/47 A61K49/14 A61K47/48 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95/34295 A (UNIV VANDERBILT) 21 December 1995 (1995-12-21) * page 6, second paragraph; page 11, first paragraph; claims 11-15 *	1-3, 5-16
Y	HEIJNE VON G ET AL: "SPECIES-SPECIFIC VARIATION IN SIGNAL PEPTIDE DESIGN IMPLICATIONS FOR PROTEIN SECRETION IN FOREIGN HOSTS" FEBS LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 244, no. 2, February 1989 (1989-02), pages 439-446, XP001149430 ISSN: 0014-5793 * page 439, left-hand column, second paragraph; page 439, right-hand column, last paragraph *	1-3, 5-16



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

10 March 2004

Date of mailing of the international search report

18/11/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Faust1, S

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/13413

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>BRAUN K ET AL: "A biological transporter for the delivery of peptide nucleic acids (PNAs) to the nuclear compartment of living cells"</p> <p>JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 318, no. 2, 2002, pages 237-243, XP002238940</p> <p>ISSN: 0022-2836</p> <p>* abstract; table 1; page 242, left-hand columns, lines 5-9 *</p> <p>-----</p>	5-10
Y	<p>BHORADE RAJEEV ET AL: "Macrocyclic chelators with paramagnetic cations are internalized into mammalian cells via a HIV-tat derived membrane translocation peptide."</p> <p>BIOCONJUGATE CHEMISTRY, vol. 11, no. 3, May 2000 (2000-05), pages 301-305, XP002242549</p> <p>ISSN: 1043-1802</p> <p>* abstract; page 301, right-hand column, lines 5-8; page 302, left-hand column, lines 1-4; figure 3 *</p> <p>-----</p>	2,12-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

NO/EP 03/13413

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9534295	A	21-12-1995	US 5807746 A	15-09-1998
			AU 2828095 A	05-01-1996
			WO 9534295 A1	21-12-1995
			US 6043339 A	28-03-2000
			US 6495518 B1	17-12-2002